PRODUCT MONOGRAPH

[Pr]TEVA-METFORMIN

(metformin hydrochloride)

500 mg and 850 mg Tablets

Teva Standard

Oral Antihyperglycemic Agent

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THERAPEUTIC CLASSIFICATION

Oral Antihyperglycemic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

TEVA-METFORMIN (metformin hydrochloride) is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effect on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or that it might enhance the effect of insulin on the peripheral receptor site. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes.

Metformin absorption is relatively slow and may extend over about 6 hours. The drug is excreted

in urine at high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5 % of the absorbed dose is slow with a half-life between 9 and 17 hours. Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1 to 2 mcg/mL. Certain drugs may potentiate the effects of metformin (see PRECAUTIONS).

A comparative, two-way, single-dose bioavailability study was conducted on two 500 mg metformin hydrochloride tablet products, TEVA-METFORMIN 500 mg and GLUCOPHAGE® 500 mg tablets. The pharmacokinetic data calculated for metformin hydrochloride in the TEVA-METFORMIN and GLUCOPHAGE® tablet formulations is tabulated below.

	Geometric Mean Arithmetic Mean (C.V.)		
	Teva-Metformin (1 X 500 mg)	Glucophage®** (1 X 500 mg)	Percentage of Glucophage®
AUC_T (ng•hr/mL)	3578 3717 (31)	3773 3917 (29)	95.8
AUC_I (ng•hr/mL)	4010 4157 (30)	4139 4285 (28)	97.9
C_{max} (ng/mL)	458.6 473.3 (26)	493.4 510.7 (28)	93.6
T_{max}* (hr)	4.00 (0.89)	4.38 (1.02)	---
$T_{½}$* (hr)	3.60 (0.82)	3.41 (0.67)	---

* For the T_{max} and $T_{½}$ parameters these are the arithmetic means (standard deviation).

** Glucophage® manufactured by Nordic Laboratories., Laval, Quebec, Canada.

INDICATIONS

To control hyperglycemia in TEVA-METFORMIN (metformin HCl) responsive, stable, mild, non-ketosis prone, maturity onset type of diabetes (Type II) which cannot be controlled by proper dietary management, exercise and weight reduction or when insulin therapy is not appropriate.

TEVA-METFORMIN (metformin HCl) can be of value for the treatment of obese diabetic patients.

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (Type I) diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin.
- In patients with a history of lactic acidosis, irrespective of precipitating factors.
- In the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of normal range. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 136 μmol/L (males), ≥ 124 μmol/L (females) or abnormal creatinine clearance) which may result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see also WARNINGS and PRECAUTIONS).
- Congestive heart failure requiring pharmacologic treatment.
- In excessive alcohol intake, acute or chronic.
- In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, TEVA-METFORMIN should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- TEVA-METFORMIN should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of

such products may result in acute alteration of renal function (see WARNINGS and PRECAUTIONS).

- In cases of cardiovascular collapse and in disease states associate with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- In patients suffering from severe dehydration.
- Known hypersensitivity or allergy to metformin HCl or any of the excipients.
- During pregnancy.

WARNINGS

Lactic acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment with TEVA-METFORMIN; when it occurs, it is fatal in approximately 50 % of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia,

are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. TEVA-METFORMIN treatment should not be initiated in patients ≥ 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as the patients are more susceptible to developing lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking TEVA-METFORMIN and by use of the minimum effective dose of TEVA-METFORMIN. In addition, TEVA-METFORMIN should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, TEVA-METFORMIN should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking TEVA-METFORMIN (metformin HCl), since alcohol intake potentiates the effect of metformin HCl on lactate metabolism. In addition, TEVA-METFORMIN should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see PRECAUTIONS). The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistance bradyarrhyhmas with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see PRECAUTIONS). TEVA-METFORMIN should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of TEVA-METFORMIN, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking TEVA-METFORMIN do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms,

such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking TEVA-METFORMIN, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin HCl is dialysable (with clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see CONTRAINDICATIONS and PRECAUTIONS).

If acidosis of any kind develops, TEVA-METFORMIN should be discontinued immediately.

Increased risk of cardiovascular mortality:
The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 1027 patients who were randomly assigned to one of the five treatment groups.

The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) or diet plus a fixed dose of phenformin (100 mg per day), had a rate of cardiovascular mortality approximately 2.5 times that of patients treated with diet alone, resulting in discontinuation of both these treatments in the UGDP study. Total mortality was increased in both the tolbutamide- and phenformin-treated groups and this increase was statistically significant in the phenformin-treated group. Despite controversy regarding the

interpretation of these results, the findings of the UGDP study provide and adequate basis for this warning. The patient should be informed of the potential risks and benefits of TEVA-METFORMIN and alternative modes of therapy.

Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other related antidiabetic drugs, in view of the similarities in mode of action and chemical structure among the drugs in each category.

The use of TEVA-METFORMIN (metfomin HCl) will not prevent the development of complications peculiar to diabetes mellitus.

Use of TEVA-METFORMIN must be considered as treatment in addition to proper dietary regimen and not as a substitute for diet.

Care should be taken to ensure that TEVA-METFORMIN is not given when a contraindication exists.

If during TEVA-METFORMIN therapy the patient develops acute intercurrent disease such as: clinically significant hepatic dysfunction, cardiovascular collapse, congestive heart failure, acute myocardial infarction, or other conditions complicated by hypoxemia, the drug should be discontinued.

Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography and scans with contrast materials):

Intravascular contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving TEVA-METFORMIN (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, TEVA-

METFORMIN should be discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

PRECAUTIONS

Patient Selection and Follow-up:
Careful selection of patients is important. It is imperative that there be rigid attention to diet and careful adjustment of dosage. When TEVA-METFORMIN (metformin HCl) is combined with a sulfonylurea, instruct the patient on hypoglycemic reactions and their control. Regular through follow-up examinations are necessary (see WARNINGS).

If vomiting occurs, withdraw drug temporarily, exclude lactic acidosis, then resume dosage cautiously (see ADVERSE REACTIONS).

Particular attention should be paid to short range and long range complications which are peculiar to diabetes. Periodic cardiovascular, ophthalmic, hematological, hepatic and renal assessments are advisable (see WARNINGS).

Monitoring of renal function:
TEVA-METFORMIN is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive TEVA-METFORMIN. In patients with advanced age, TEVA-METFORMIN should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and generally, TEVA-METFORMIN should not be titrated to the maximum dose (see DOSAGE AND ADMINISTRATION).
Before initiation of TEVA-METFORMIN therapy and every 6 months while on TEVA-

METFORMIN therapy, renal function should be assessed and verified as being within normal range.
In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and TEVA-METFORMIN discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition:
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with disposition of TEVA-METFORMIN, such as cationic drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution.

Hypoxic states:
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such event occur in patients on TEVA-METFORMIN therapy, the drug should be promptly discontinued.

Surgical Procedures:
TEVA-METFORMIN therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). TEVA-METFORMIN should be discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake:
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving TEVA-METFORMIN.

Impaired hepatic function:
Since impaired hepatic function has been associated with some cases of lactic acidosis, TEVA-METFORMIN should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels:
Impairment of vitamin B_{12} and folic acid absorption has been reported in some patients. Therefore, measurements of serum vitamin B_{12} and folic acid are advisable at least every one to two years in patients on long-term treatment with TEVA-METFORMIN.

A decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7 % of patients receiving metformin HCl in controlled clinical trials of 28 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from B_{12}-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin HCl or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on TEVA-METFORMIN and any apparent abnormalities should be appropriately investigated and managed (see LABORATORY TESTS). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

Change in clinical status of previously controlled diabetic:
A diabetic patient previously well controlled on TEVA-METFORMIN who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, TEVA-METFORMIN must be stopped

immediately and appropriate corrective measures initiated (see WARNINGS).

Hypoglycemia:
Hypoglycemia does not occur in patients receiving TEVA-METFORMIN alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose lowering agents (such as sulfonylureas) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose:
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold TEVA-METFORMIN and temporarily administer insulin. TEVA-METFORMIN may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with TEVA-METFORMIN or sulfonylurea monotherapy, combined therapy with TEVA-METFORMIN (metformin HCl) and sulfonylurea may result in a response. Should secondary failure occur with combined TEVA-METFORMIN/sulfonylurea therapy, it may be necessary to initiate insulin therapy.

Laboratory tests:
Response to all diabetic therapies should be monitored by periodic measurements of fasting

blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see DOSAGE AND ADMINISTRATION).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with TEVA-METFORMIN (metformin HCl) therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Pregnancy and lactation:
Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing mother:
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
Controlled clinical studies of metformin HCl did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. TEVA-METFORMIN is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function (see CONTRAINDICATIONS and WARNINGS). Because aging is associated with reduced renal function, TEVA-METFORMIN should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring or renal function. Generally, elderly patients should not be titrated to the maximum dose of TEVA-METFORMIN.

Drug Interactions:
Certain drugs may potentiate the effect of TEVA-METFORMIN, particularly sulfonylurea type of drugs in the treatment of diabetes. The simultaneous administration of these two types of drugs could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol.

In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with

highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to serum proteins.

Glyburide:

In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamics effects, makes the clinical significance of this interaction uncertain.

Furosemide :

A single dose study, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22 % and blood AUC by 15 %, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31 % and 12 % smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32 %, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine:

A single-dose, metformin-nifedipine drug interaction study in healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20 % and 9 %, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs:

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine,

triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such an interaction has been observed between metformin and oral cimetidine in normal healthy volunteers in both single and multiple-dose, metformin-cimetidine drug interaction studies, with a 60 % increase in peak metformin plasma and whole blood concentrations and a 40 % increase in plasma and whole blood metformin AUC was observed. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Therefore, careful patient monitoring and dose adjustment of TEVA-METFORMIN or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion.

Other:
Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to patients receiving TEVA-METFORMIN, the patient should be closely observed to maintain adequate glycemic control.

Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20 % when used concurrently with TEVA-METFORMIN. Therefore, patients receiving phenprocoumon or other antivitamin K anticoagulants should be monitored carefully when both types of drugs used simultaneously. In such cases, an important increase of prothrombin time may occur upon cessation of TEVA-METFORMIN therapy, with an increased risk of hemorrhage.

> **NOTE**: When used as indicated, there has not been a single case of lactic acidosis in Canada. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patients/year with

approximately 0.015 fatal cases/1000 patients/year). TEVA-METFORMIN should be immediately discontinued in the presence of acidosis.

Physicians should instruct their patients to recognize the symptoms which could be signal onset of lactic acidosis (see WARNINGS).

ADVERSE REACTIONS

Lactic Acidosis:

See WARNINGS, PRECAUTIONS, and OVERDOSAGE Sections.

Gastrointestinal Reactions:

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to TEVA-METFORMIN and are approximately 30 % more frequent in patients on TEVA-METFORMIN monotherapy than in placebo-treated patients, particularly during initiation of TEVA-METFORMIN therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take TEVA-METFORMIN (metformin HCl) with meals (see DOSAGE and ADMINISTRATION).

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, TEVA-METFORMIN should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on TEVA-METFORMIN, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses:

During initiation of TEVA-METFORMIN therapy, approximately 3 % patient may complain of an unpleasant or metallic taste, which usually resolves spontaneously.

Dermatologic Reactions:

The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for metformin monotherapy and to sulfonylurea for metformin /sulfonylurea therapy.

Hematologic:

During controlled clinical trials of 29 weeks duration, approximately 9 % of patients on metformin HCl monotherapy and 6 % of patients on metformin HCl sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed. Therefore, serum vitamin B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered (see also PRECAUTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Available information concerning treatment of a massive overdosage of metformin is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

Hypoglycemia has not been seen even with ingestion of up to 85 grams of metformin, although lactic acidosis has occurred in such circumstances (see WARNINGS). Metformin is dialysable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE AND ADMINISTRATION

In diabetic patients, individual determination of the minimum dose that will lower blood glucose adequately should be made.

In patients where on initial trial the maximal recommended dose fails to lower the blood glucose adequately, the drug should be discontinued. Deterioration of the patient's condition can occur during the treatment of diabetes. It is advisable to ascertain the contribution of the drug in the control of blood glucose by discontinuing the medication semi-annually or at least annually with careful monitoring patient. If the need for the drug is not evident, the drug should not be resumed. In some diabetic subjects, short-term administration of the drug may be sufficient during periods of transient loss of blood sugar control.

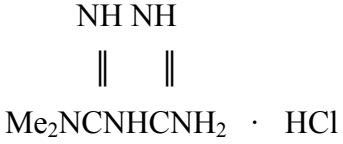
The usual dose is 500 mg three or four times a day, or 850 mg two or three times a day. Maximal dose should not exceed 2.55 g a day. To minimize gastric intolerance such as nausea and vomiting TEVA-METFORMIN (metformin HCl) should be taken with food whenever possible.

PHARMACEUTICAL INFORMATION

Proper Name: Metformin Hydrochloride

Chemical Name: 1, 1-Dimethylbiguanide hydrochloride

Structural Formula:



Molecular Formula: $C_4H_{11}N_5 \cdot HCl$

Molecular Weight: 165.6

Physical Form: Metformin HCl is a white crystalline powder.

Solubility: Metformin HCl is soluble in water and in 95 % ethyl alcohol. It is practically insoluble in ether and in chloroform.

Melting Point: 225°C.

COMPOSITION

TEVA-METFORMIN 500 mg Tablet contains 500 mg metformin HCl. Each tablet also contains as non-medicinal ingredients: colloidal silicon dioxide, corn starch, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, Opadry Y-1-7000H White (colour composition: hypromellose, macrogol and titanium dioxide).

TEVA-METFORMIN 850 mg Tablet contains 850 mg metformin HCl. Each tablet also contains

as non-medicinal ingredients: corn starch, pregelatinized starch, colloidal silicon dioxide, sodium starch glycolate, microcrystalline cellulose and magnesium stearate.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C - 30°C. Unit dose strips should be stored between 15°C - 25°C and protected from high humidity.

AVAILABILITY

TEVA-METFORMIN (metformin HCl) 500 mg tablets are white to off-white, round, bi-convex bevel-edged coated tablets, engraved modified N deep bisect modified N on one side and 500 on the reverse. Bottles of 100 and 500 tablets.

TEVA-METFORMIN (metformin HCl) 850 mg tablets are white, oval shaped bi-convex compressed tablets engraved modified N on one side and 850 on the reverse. Bottles of 100, 500, 1000 tablets and boxes of 100 tablets as unit dose strips.

PHARMACOLOGY

Metformin absorption is relatively slow and may extend over about 6 hours.

Animal studies with metformin, labeled with ^{14}C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands.

It has been shown that, following a 2 g dose of metformin, the blood level remains under 10 mcg/mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes, is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin:
Metformin improves the K co-efficient of glucose assimulation.
Metformin improves the co-efficient of insulin efficiency.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defense mechanism tending to mobilize body reserves in order to combat hypoglycemia.

In the diabetic animal with a low liver glycogen reserve, the opposite occurs and metformin builds up glycogen stores of the liver. In vitro, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethyl-biguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metformin is eliminated in faeces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

Metabolites of metformin have not been identified, neither by radio-active nor by chemical methods.

A single Rf spot is always present following radiochromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine lactate or pyruvate. However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal species and design of experimental model.

This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malasorption phenomenon has been observed with biguanides under certain experimental conditions in animal and in man. In one study, a 20 % retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl-CoA generation.

However, inhibition of insulin-stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl-CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect exerted by these drugs in obese diabetic patients.

TOXICOLOGY

1. **Animal Toxicity**

Acute Toxicity (LD_{50})

Animal	Subcutaneously	Orally
Mouse	225 mg/kg	3500 mg/kg
Chicken	150 mg/kg	
Rat	300 mg/kg	1000 mg/kg
Rabbit	150 mg/kg	350 mg/kg
Guinea Pig	150 mg/kg	500 mg/kg

Chronic Toxicity

A) The following doses of metformin produced no organ toxicity:

Rats	125 mg/kg	per os for one year
Rabbits	100 mg/kg	per os for one year
Dogs	50 mg/kg	subcutaneously for 2 years

Acute or chronic organ toxicity was not produced in the animal species involved.

B) A study was carried out during 9 months with 80 rats, male and female, divided in 4 groups, with the following dosage regimen:

1st Group	control
2nd Group	150 mg/kg per os
3rd Group	300 mg/kg per os
4th Group	300 mg/kg per os, dose increased by 100 mg/kg/day every 15 days

In summary, the authors report the excellence tolerance of metformin by rats, even when administered in very high doses. No drug related lesion has been observed.

C) Chronic toxicity studies of 9 months duration were carried through with 16 beagle dogs, although the complete intolerance of this animal species to oral

hypoglycemic agents is a well established fact. Trophic and neurologic disorders with cachexia rapidly lead to the dog's death. During the periods of metformin administration, laboratory findings were within normal limits. The levels of enzymes were somewhat elevated, but it is difficult to ascribe a pathological significance to their values, since subjects in the control group were at the same level as treated animals.

Pathological studies show an extreme degree of undernutrition in all metformin treated animals. Profound wasting especially marked in fat tissues was evident in all organs. Cachexia appears as the common cause of death of these animals.

2. **Human Toxicity**

In man, no adverse effect has been reported on liver or kidney function, the hematopoietic system or on the blood vessels.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases /1000 patients/year with approximately 0.015 fatal cases/1000 patients/year).

The consecutive administration of both phenformin and metformin to the same patient has allowed for the demonstration of a fundamental difference between these two biguanides in relation to lactacidemia. In some instances, patients developed hyperlactacidemia with phenformin when the same patients were presenting normal lactic acid levels while being treated with metformin. In other instances, hyperlactacidemia observed during a treatment with phenformin did regress when metformin was substituted for phenformin. Metformin may increase lactacidemia but to a degree that is clinically less significant than the elevation seen after phenformin.

3. **Teratology**

Teratological studies were carried out in albino rats divided in three groups:

No abnormalities were found, even when high doses were administered. The number of animals was the same in each group.

Death rate in the three groups of treated animals and controls was approximately the same. However, the number of living animals in each group treated was slightly lower than in the control group. Also, the frequency of litters exceeding 10 live animals was slightly higher in the control group. A loss of weight at the time of weaning has been observed when compared to the control group.

Nevertheless, on a statistical basis, differences were shown to be non-significant. There is no difference between the groups of treated animals and the control group regarding the number of stillborn. The number of deaths after birth was slightly higher in metformin treated groups than in the control group, but the comparison of average death rates is not significant ($p < 0.05$).

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